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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,573	02/08/2001	Etienne Regulier	017753-137	5075

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,573	REGULIER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 33-57 are pending.

Applicants' traversal, the amendment to claim 33, the cancellation of claims 1, 7, 11-15, 19, and 25-32, the addition of claims 41-57 in paper filed on 11/23/04 is acknowledged and considered.

Claim Objections

Claims 54 and 57 are objected to because of the following informalities:

A claim, which depends from a dependent claim, should not be separated by any dependent claim, which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-40 remain and claims 41-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33-40 and new claims 41-44 filed on 11/23/04 introduce new subject matter into the application.

The application and the originally filed claims as a whole are directed to a composition comprising: (i) a nucleic acid sequence encoding all or part of an MIP chemokine, (ii) at least one nucleic acid sequence encoding IL-2, said nucleic acid sequence being placed under the control of elements required for the expression in a host cell of said mammal and using the composition to treat a proliferative disorder in a patient.

The original specification and claims do not disclose the limitation, "wherein the IL-2 and MIP chemokine work together synergically to inhibit the growth or cause the rejection of a tumor in said patient when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequence (i) or the nucleic acid sequence (ii)" in the claims and new claims. The pages cited for support of the limitation in claims 33-40 and the new claims 41-44 do not provide support for the limitation. See Pages 29-32 in the examples and Figures 1-6. The specification recites, "We have now identified novel cytotoxic compositions in which the various constituents are chosen so to obtain a synergistic effect of their respective activities and improved properties of said constituents" (Page 3, lines 17-20). However, the specification does not describe what is a synergistic effect and does not specifically point out what cytotoxic composition produces a synergistic effect. In addition, the instant specification does not describe the term synergically. Furthermore, the working examples do not disclose a composition comprising a nucleic acid sequence encoding an MIP chemokine

or a natural variant thereof and a nucleic acid sequence encoding IL-2, wherein the IL-2 and MIP chemokine work together synergically compared to a composition comprising the a vector comprising only the nucleic acid sequence encoding IL-2 or a vector comprising only the nucleic acid sequence encoding MIP. It is apparent that the applicants at the time the invention was made did not intend or contemplate the claimed invention as part of the disclosure of their invention. There is no evidence in the specification that the applicants were possession of the claimed method, where IL-2 and MIP chemokine working together synergically, at the time the application was filed.

Applicants' arguments filed 11/23/04 have been fully considered but they are not persuasive.

With respect to applicants' argument that the subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy requirement (See MPEP 2163.02), the argument is not found persuasive because the specification does not reasonably convey to the skilled artisan that the inventor had possession at that time of the later claimed subject matter. Furthermore, the assertion by applicant that the subject matter of the claim need not be described literally in order for the disclosure to satisfy the requirement indicates that the limitation is not support by the specification as filed.

With respect to applicants' argument that the skilled artisan would consider the experiments shown in Figure 2 in its general context, and there may be some divergence between individual animals, the argument is not found persuasive because other than the assertion, the applicants provide no guidance and/or evidence to support these assertions. Therefore, applicants' assertions are not compelling. See MPEP § 716.01(c).

With respect to applicants' figures 3 and 4 clearly exhibit a synergistic effect, as the mice receiving both components had a markedly greater life span compared to mice that only received on component, the argument is not found persuasive because the figures do not clearly exhibit a synergistic effect.

Tumor development in figure 3 is not clearly inhibited in mice treated with nucleic acid sequences encoding both IL-2 and MIP-1 beta because the average tumor volume was $500mm^3$. It is unclear to one skilled in the art how tumor development can be clearly inhibited if the average tumor volume was $500mm^3$. Furthermore, figure 3 displays that the average tumor volume for the combination of IL2 and MIP1beta was $500mm^3$ compared to the average tumor volume for IL2 alone ($700\text{-}1000mm^3$) and MIP1beta ($4000mm^3$). The figure indicates an additive effect for the combination and not a synergistic effect for the combination. Thus, the figure does not provide support for the limitation.

The measurement of survival rate in Figure 4 displays IL-2 and the combination of IL-2 and MIP1beta have the same survival rate at 50 days and at 100 days the combination has a higher survival rate (36%) compared to the survival rate for IL-2 alone (14%).

Furthermore, figures 3 and 4 are only directed to MIP1beta and IL-2 and do not display any results for a synergistic effect for the combination of MIP1alpha and IL-2 or other MIP chemokines.

With respect to applicants' argument that Figures 5 and 6 display a synergistic effect for the combination of a MIP chemokine and IL-2, the argument is not found persuasive because the figures display different combinations of anti-tumor agents and do not compare the combination of a MIP chemokine and IL-2 to either a MIP chemokine or IL-2. The specification and the prior

art do not provide support for the skilled artisan to reasonably conclude that the limitation is supported by the figures. For these reasons, the applicants do not provide any evidence of record that one skilled in the can correlate that these figures provide support for the claimed method.

With respect to applicants' argument that the specification throughout states that the present invention is directed to a composition comprising a mixture of two distinct constituents that together provide a cytotoxic effect (e.g., an anti-tumor activity) (see page 6, lines 13-23), the argument is not found persuasive because the applicants do not describe to one skilled in the art how the teachings in the specification would provide support for the limitation 'wherein the IL-2 and MIP chemokine work together synergically to inhibit the growth or cause the rejection of a tumor in said patient when compared to the anti-tumor response in said patient administered with a composition comprising a vector comprising only the nucleic acid sequence (i) or the nucleic acid sequence (ii).'

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 45-47 and 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boursnell et al. (US Patent 6,287,557) taken with Hobart et al. (US Patent 5,147,055) and LaFace (US 6,649,158) and Song et al., (J.Exp. Med., 186:1247-1256, 1997).

Boursnell teaches virus vectors encoding nucleotide sequences expressing immunomodulating proteins including cytokines and chemokines and combinations thereof (col. 6, lines 55-67), such as IL-2 and MIP1β (col. 7, lines 1-11) for cancer immunotherapy, wherein each of the sequences are placed under control of a known viral promoter or a mammalian specific promoter (col. 9, lines 45-51). Boursnell further teaches making and using a vector comprising two or more nucleotide sequences or a mixture of two vectors containing at least one gene encoding a different immunomodulator product (col. 8, lines 50-55). Furthermore, Boursnell teaches a method of using the vector for cancer immunotherapy in an animal by direct administration (col. 11, lines 8-67). The vector can be a mutant DNA or RNA virus, e.g.,

adenovirus, poxvirus (col. 5, lines 49-55). The vectors used in the method taught by Boursnell are in pharmaceutically acceptable formulas.

However, Boursnell does not specifically teach using a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding a MIP1-beta to inhibit tumor growth or cause the rejection of a tumor in a patient in need thereof. In addition, Boursnell does not specifically teach using a composition comprising at least two nucleotide sequences encoding IL-2 and a nucleotide sequence encoding a MIP1-beta. In addition, Boursnell does not specifically teach inserting the nucleic acid sequences into either the same vector or a distinct vector.

However, at the time the invention was made, Hobart teaches a method of treating a solid tumor in an animal comprising introducing a vector comprising IL-2 into the solid tumors (col. 4, lines 33-41, col. 4, line 66- col. 5, and col. 33, line 33 to col. 36, line 37).

In addition, at the time the invention was made, LaFace teaches that MIP-1.beta. is a dendritic cell chemoattractant (DCC) that induces chemotaxis of mature dendritic cells (columns 11-12). Song teaches that dendritic cells are potent antigen-presenting cells that play a critical role in the initiation of an anti-tumor immune response (page 1247).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Boursnell taken with Hobart and LaFace and Song to make and use a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding an MIP1-beta to inhibit tumor growth in a patient. One of ordinary skill in the art would have been motivated to combine the teachings because a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence

encoding MIP1β were well known to one of ordinary skill in the art for treating tumors in an animal. Therefore, it would have been obvious to one of ordinary skill in the art to make and use the composition in a method of treating a tumor in a patient in need.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Boursnell taken with Hobart and LaFace and Song to insert a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding MIP1β into the same vector. One of ordinary skill in the art would have been motivated to insert both sequences into the same vector to simplify delivering the sequences to a cell and because Boursnell teaches that it was routine to one of ordinary skill in the art to use one vector comprising two different nucleotide sequences in a cancer immunotherapy method.

Furthermore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Boursnell taken with Hobart and LaFace and Song to insert a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding MIP1β into distinct vectors. One of ordinary skill in the art would have been motivated to insert both sequences into different vectors because Boursnell teaches that it was routine to one of ordinary skill in the art to use two different vectors comprising two different nucleotide sequences in a cancer immunotherapy method.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Boursnell taken with Hobart and LaFace and Song to make a composition comprising a nucleotide sequence encoding IL-2 and a nucleotide sequence encoding a MIP1β, wherein the composition is inserted into a recombinant adenovirus vector. One of ordinary skill in the art would have been motivated to combine the teachings

because recombinant adenoviral vectors comprising an anti-tumor gene were well known to one of ordinary skill in the art for reducing tumors in an animal. Therefore, it would have been obvious to one of ordinary skill in the art to make and use the adenoviral vector comprising the nucleotide sequences in a cancer immunotherapy method.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 45, 50-54, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boursnell et al. (US Patent 6,287,557) taken with Hobart et al. (US Patent 5,147,055) and LaFace (US 6,649,158) and Song et al., (J.Exp. Med., 186:1247-1256, 1997) as applied to claims 45-47 and 49-50 above, and further in view of in further view of Bruder et al. (US Patent 6,440,944).

Boursnell taken with Hobart and LaFace and Song do not specifically teach making a replication defective adenoviral vector, wherein said adenoviral vector is deleted in the E1 region, or E1 and E4, or E1 and E3, or E1, E3, and E4.

However, at the time the invention was made, replication defective adenoviral vectors were well known to one of ordinary skill in the art for gene delivery because they are superior vehicles for transferring genetic material to a wide variety of cells and represent a safe choice of gene transfer. Bruder teaches that a variety of recombinant adenoviral vectors are known in the art for gene delivery (col. 1, lines 34-55). Bruder teaches an adenoviral vector with a gene of interest inserted into the E1 region of the adenovirus. Furthermore, Bruder teaches multiply deficient adenoviral vectors that are deficient in E1, E3 and E4. One of ordinary skill in the art

understands that a recombinant adenoviral vector is replication defective because genes essential for adenovirus replication are deleted.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make and use a replication defective adenoviral vector taught by Bruder in the method taught by Boursnell taken with Hobart and LaFace and Song. One of ordinary skill in the art would have been motivated to use a replication defective adenoviral vector because they are superior vehicles for transferring genetic material to a wide variety of cells and represent a safe choice of gene transfer. In addition, one of ordinary skill in the art would have been motivated to use a multiply deficient adenoviral vector (E1-; E1-E4-; and E-1, E3-) to abolish expression of the adenoviral proteins (E1, E3, and/or E4) to improve the delivery of exogenous nucleic acid sequences to an animal.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 45, 55, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boursnell et al. (US Patent 6,287,557) taken with Hobart et al. (US Patent 5,147,055) and LaFace (US 6,649,158) and Song et al., (J.Exp. Med., 186:1247-1256, 1997) as applied to claims 45-47 and 49-50 above, in further view of Gruber (US Patent 6,410,326).

Boursnell taken with Hobart and LaFace and Song do not specifically teach making a poxvirus vector selected from the group consisting of vaccinia virus, MVA, and canary pox.

However, at the time the invention was made, vaccinia virus was well known to one of ordinary skill in the art for expressing heterologous proteins at high levels as taught by Gruber (col. 7, line 65, col.8, line 26).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to make and use vaccinia virus taught by Gruber in the method taught by Boursnell taken with Hobart and LaFace and Song. One of ordinary skill in the art would have been motivated to make and use a vaccinia viral vector because vaccinia virus vectors were well known to one of ordinary skill in the art for expressing heterologous proteins at high levels in cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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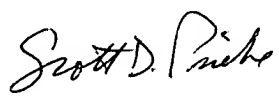
Brian Whiteman
Patent Examiner, Group 1635



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